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Pharmacological effects of biotin☆

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Abstract

In the last few decades, more vitamin-mediated effects have been discovered at the level of gene expression. Increasing knowledge on the molecular mechanisms of these vitamins has opened new perspectives that form a connection between nutritional signals and the development of new therapeutic agents. Besides its role as a carboxylase prosthetic group, biotin regulates gene expression and has a wide repertoire of effects on systemic processes. The vitamin regulates genes that are critical in the regulation of intermediary metabolism: Biotin has stimulatory effects on genes whose action favors hypoglycemia (insulin, insulin receptor, pancreatic and hepatic glucokinase); on the contrary, biotin decreases the expression of hepatic phosphoenolpyruvate carboxykinase, a key gluconeogenic enzyme that stimulates glucose production by the liver. The findings that biotin regulates the expression of genes that are critical in the regulation of intermediary metabolism are in agreement with several observations that indicate that biotin supply is involved in glucose and lipid homeostasis. Biotin deficiency has been linked to impaired glucose tolerance and decreased utilization of glucose. On the other hand, the diabetic state appears to be ameliorated by pharmacological doses of biotin. Likewise, pharmacological doses of biotin appear to decrease plasma lipid concentrations and modify lipid metabolism. The effects of biotin on carbohydrate metabolism and the lack of toxic effects of the vitamin at pharmacological doses suggest that biotin could be used in the development of new therapeutics in the treatment of hyperglycemia and hyperlipidemia, an area that we are actively investigating.

Keywords: Biotin; Carbohydrates; Lipids; Gene expression; Carboxylases; Glucokinase

In the last few decades, more vitamin-mediated effects have been discovered at the level of gene expression [1–3] in addition to their well-known roles as substrates and cofactors [4]. The best recognized examples are the lipophilic Vitamins A and D that serve as ligand precursors of the hormone nuclear receptors superfamily and thus affect systemic functions such as morphogenesis, immunity, growth and epithelial cell differentiation [1–3]. Increasing knowledge on the molecular mechanisms of these vitamins has opened new perspectives that form a connection between nutritional signals and the development of new therapeutic agents [5,6]. Although little is known about water-soluble vitamins as genetic modulators, there are increasing examples of their effects on gene expression [7–9].

Biotin is a hydrosoluble vitamin that acts as a prosthetic group of carboxylases. Unrelated to its role as carboxylase prosthetic group, biotin regulates gene expression [9,10] and has a wide repertoire of effects on systemic processes such as development [11,12] and immunity [13,14].

The first evidence that biotin affects glucose metabolism was reported by Dakshinamurti et al. [15] in biotin-deficient rats. They observed that glucose tolerance test curves in biotin-deficient rats were significantly higher than those in nondeficient rats, as well as glucose phosphorylation and incorporation into glycogen in the liver [15]. They further demonstrated that these effects were the result of a reduction in the activity of hepatic glucokinase [16], a critical enzyme that regulates glucose uptake in the liver. It has now been well established that the effect of biotin on liver glucokinase activity is not limited to biotin-deficient rats and that such stimulation is observed in rats receiving adequate and pharmacological concentrations of biotin in the diet [16]

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as well as in diabetic rats [17]. The effect of biotin on glucokinase is also observed in cultured rat hepatocytes [18] and appears to be mediated through biotin-induced increases of cyclic GMP [18]. Later, with the arrival of molecular biology techniques, Chauhan and Dakshinamurti [19] demonstrated that the stimulatory effect of biotin occurs at the level of transcription. This important discovery set the hallmark on the studies of the role of biotin in gene expression.

Since the finding that biotin increases hepatic glucokinase transcription [19], significant progress has been made in the identification of genes whose expressions are affected by biotin (reviewed in Ref. [9]). The vitamin regulates genes that are critical in the regulation of intermediary metabolism. We [20] found that biotin stimulates the expression of insulin and pancreatic glucokinase, an enzyme that plays an important role in glucose homeostasis regulating insulin secretion in response to changes in blood glucose concentrations. Our studies found that biotin concentrations of 10 to 1000 nM augmented glucokinase activity and mRNA abundance in cultured pancreatic islets isolated from non-biotin-deficient rats [20]. A similar stimulatory effect on pancreatic glucokinase was observed in the insulinoma RIN 1046-38 cell line [21]. We also found that insulin expression and secretion were increased in response to biotin [20]. On the other hand, we found that biotin deficiency decreased pancreatic glucokinase activity and mRNA abundance: Islets isolated from biotin-deficient rats showed about half of the glucokinase activity and mRNA levels observed in control rats. Furthermore, insulin secretion in response to glucose was also impaired in islets isolated from deficient rats [20]. Another essential protein involved in intermediary metabolism, insulin receptor, has also been shown to be regulated by biotin: In the hepatoblastoma cell line HuH7, De la Vega and Stockert [22] found that biotin increased the insulin receptor at the posttranscriptional level; they also found that this effect required the activation of the cGMP signal cascade. Contrary to its stimulatory effects on genes whose action favors hypoglycemia (insulin, insulin receptor, pancreatic and hepatic glucokinase), biotin decreases the expression of hepatic phosphoenolpyruvate carboxykinase [23], a key gluconeogenic enzyme that stimulates glucose production by the liver and thus opposes the glucose catabolic pathways involving hepatic glucokinase.

As can be expected due its role as a prosthetic group of carboxylases, biotin availability modulates the activity of pyruvate carboxylase (PC), a pivotal enzyme in anapleroris and gluconeogenesis, and acetyl–CoA carboxylases 1 and 2 (ACC 1, ACC 2), two enzymes that regulate fatty acid synthesis and oxidation, respectively. In addition, biotin also regulates the genetic expression of these enzymes at the mRNA level in the case of ACC 1 [24] and at the posttranscriptional level in the case of PC [25].

The findings that biotin regulates the expression of genes that are critical in the regulation of intermediary metabolism are in agreement with several observations that indicate that biotin supply is involved in glucose and lipid homeostasis.

Biotin deficiency has been linked to impaired oral glucose tolerance tests and decreased utilization of glucose in rats [15,26]. In diabetic patients, it has been found that the biotin status is also altered. Studies by Maebashi et al. [27] in Type 2 diabetic patients found that serum biotin concentration was lower than in control subjects. An inverse correlation between serum biotin and fasting blood glucose concentration has also been observed [27,28]. However, we found that lymphocyte PCC activity, currently considered a more accurate indicator than plasma biotin concentration [29,30], did not differ significantly between mild hyperglycemic Type 2 diabetic patients and nondiabetic subjects [31]. In this work, we also found that pharmacological doses of 15 mg/day of biotin increased lymphocyte PC, ACC and PCC activities. Twenty-eight days of treatment in subjects, either diabetic or nondiabetic, who received biotin increased PCC and ACC activities by approximately 100% and PC activity by approximately 200%.

On the other hand, biotin excess appears to ameliorate the diabetic state. In genetically diabetic KK mice and in OLETF rats, biotin treatment lowered postprandial glucose concentration and improved tolerance to glucose [32,33]. The hypoglycemic effect of the vitamin has also been observed in humans. Reduced hyperglycemia was observed in a group of Type 1 diabetic patients receiving 16 mg/day of biotin for 1 week [28]. This improvement has also been observed in Japanese Type 2 diabetic patients in whom a decrease of about 45% hyperglycemic fasting blood glucose concentrations was observed after 1 month of treatment with oral doses of 9 mg/day of biotin [27]. In hemodialysis patients, pharmacological doses of biotin improved their oral glucose tolerance tests [34]. Studies in our laboratory [35] found that 28 days of treatment with 15 mg of biotin decreased glucose and insulin concentrations.

Several studies have reported a relationship between biotin and lipid metabolism [36–40]. Spontaneous symptoms of biotin deficiency were detected in rats genetically prone to development of elevated blood lipids [36]. In this rat strain, an inverse association was found between plasma lipids and biotin status [37]. A negative correlation between plasma biotin concentrations and blood lipids was also found in humans [38]. Furthermore, pharmacological doses of biotin modify plasma lipid concentrations: A decrease in plasma lipids was observed in humans within 30 min of infusion of 100 mg of biotin [39]. In healthy volunteers, oral biotin supplementation affected plasma lipid concentrations [39]. In patients with atherosclerosis and hyperlipidemia, Dukusova and Krivoruchenko [40] found that the administration of 5 mg/day of biotin for 4 weeks decreased hypercholesterolemia. We [31] found that biotin treatment (15 mg/day) for 28 days decreased hypertriglyceridemia in all subjects (four diabetics and one nondiabetic) whose triacylglycerol concentrations were higher than 25% above

the normal standard of 1.80 mmol/L. These observations support the concept that biotin is able to decrease exacerbated hyperlipidemia.

Little is known about the effects of pharmacological doses of biotin on the expression of lipid metabolism enzymes. In rats, Lewis et al. [41] found that in rats consuming a diet containing 100 mg/kg of biotin during 21 days, the abundance of biotinylated ACC 2 but not that of ACC 1 mass significantly reduced. ACC 2 inhibition has been shown to lead to a decrease in malonyl–CoA levels and the disinhibition of fatty acid oxidation [42]. Therefore, it may be possible that pharmacological doses of biotin increase fatty acid oxidation by decreasing ACC 2 activity.

The notion that a vitamin can be used as a therapeutic agent is not new (e.g., niacin has been used since 1955 as a lipid-lowering drug beyond its role as a vitamin) [43,44]. Furthermore, extensive research on the molecular mechanisms of lipophilic Vitamins A and D has opened new perspectives that connect nutritional signals and the development of new therapeutic agents [5] including promising candidates in diabetes treatment [45,46]. It is only until recently that the molecular action of biotin and its effects on different metabolic functions have attracted attention. The important role of biotin in systemic functions is being reconsidered with the help of new technologies and with novel results regarding the molecular mechanisms of this vitamin, and, as with Vitamins A and D, this might lead to new perspectives in the development of therapeutic agents. The effects of biotin on carbohydrate metabolism and the lack of toxic effects of the vitamin at pharmacological doses suggest that biotin could be used in the development of new therapeutics in the treatment of hyperglycemia and hyperlipidemia, an area that we are actively investigating.

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